

# Attention Deficit Hyperactivity Disorder (ADHD)

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ADHD - most common emotional, cognitive, and behavioral disorder pediatricians, family physicians, neurologists, and psychiatrists treat in children!

Gr. *aprosexia* - "attentional disturbance" or "failure to heed".

## CLINICAL FEATURES

Term "attention deficit" is misleading

- rather than too little attention, many patients pay **too much attention to too many things**, leading them to have little focus.
- patients have **difficulty regulating attention; difficulty inhibiting attention to nonrelevant stimuli**, and/or focusing too intensely on specific stimuli to exclusion of what is relevant.

6 major TASKS OF EXECUTIVE FUNCTION that are most commonly distorted:

- 1) **flexibility** (i.e. shifting from one mindset or strategy to another)
- 2) **organization** (e.g. anticipating both needs and problems)
- 3) **planning** (e.g. goal setting)
- 4) **working memory** (i.e. receiving, storing, then retrieving information within short-term memory)
- 5) **separating affect from cognition** (i.e. detaching one's emotions from one's reason)
- 6) **inhibiting and regulating verbal and motoric action** (e.g. jumping to conclusions too quickly, difficulty waiting in line in appropriate fashion).

**Diagnosis is clinical** (at present, no laboratory studies, imaging studies, or procedures help with diagnosis of ADHD)!

Short attention span, difficulty concentrating, impulsivity, distractibility, excitability, hyperactivity

All of following **DSM-IV criteria** for ADHD must be present:

1. Either criteria for **inattention** or criteria for **hyperactivity/impulsivity** must be met:

**Inattention:** at least 6 of 9 symptoms must have persisted for at least 6 months to degree that is *maladaptive and inconsistent with patient's developmental level*:

- 1) often does not give close attention to details or makes **careless mistakes** in schoolwork, work, or other activities.
- 2) often has **difficulty sustaining attention** in tasks or play activities.
- 3) often **does not seem to listen** when spoken to directly.
- 4) often **does not follow through with instructions** and **does not finish schoolwork**, chores, or duties in workplace (not because of oppositional behavior or failure to understand instructions).
- 5) often has **difficulties with organizing tasks** and activities.
- 6) often avoids, **dislikes**, or is reluctant to engage in homework that requires **sustained mental effort**.
- 7) often **loses things necessary for tasks** or activities (e.g. school assignments, pencils, books, tools, toys).
- 8) often is **easily distracted** by extraneous stimuli.
- 9) often is **forgetful** in daily activities.

**Hyperactivity/impulsivity:** at least 6 of 9 symptoms have persisted for at least 6 months to degree that is *maladaptive and inconsistent with patient's developmental level*:

- 1) often **fidgets** with hands or feet or squirms in seat.
- 2) often **leaves seat** in classroom or in other situations in which remaining seated is expected.
- 3) often **runs around or climbs excessively** in situations in which this behavior is inappropriate (adolescents or adults may be limited to subjective feelings of restlessness).
- 4) often has **difficulty playing** or engaging in leisure activities **quietly**.
- 5) often on go or often **acts as if driven by motor**.
- 6) often **talks excessively**.
- 7) often **blurts out answers to questions before questions** are completed.
- 8) often has **difficulty waiting turns**.
- 9) often **interrupts** or intrudes on others (e.g. butts into conversations or games).

2. **Onset** occurs no later than age of **7 years**, *most commonly before age 4 yrs*

3. Symptoms must be present in **≥ 2 situations** (e.g. school, work, home), i.e. symptoms are **pervasive**; however, may not all occur in all settings.

*communication with teachers, special educators, psychologists, parents must occur to explore all settings*

4. Disturbance causes clinically **significant distress or impairment** in social, academic, or occupational function.

5. Behavior does not occur exclusively during course of pervasive developmental disorder, premenstrual dysphoric disorder, schizophrenia, or other psychotic disorder. No mood, anxiety dissociative, or personality disorder accounts for behavior.

- child usually seems most awake in late evening (awakening child for school causes major problems).
- **hyperactivity** is defined subjectively - increase in motor activity to level that interferes with child's functioning.
- ADHD girls have lower rates of disruptive behavior (than boys).
- clumsiness and learning disability are secondary features! (but only ≈ 30% ADHD children are learning-disabled)
- significant **psychiatric comorbidity** - 50-60% patients meet DSM criteria for at least 1 coexisting condition (learning disorders, restless-legs syndrome, ophthalmic convergence insufficiency, depression, anxiety disorder, antisocial personality disorder, substance abuse disorder, conduct disorder).
- no **somatic comorbidities** are significantly associated with ADHD.

DSM-IV distinguishes three types:

1. ADHD, predominantly **inattentive** type (20-30%; boys ≈ girls)

2. ADHD, predominantly **hyperactive-impulsive** type (< 15%; boys >> girls)

3. ADHD, **combined** type (50-75%)

N.B. symptoms of attention deficit disorder may exist with or without hyperactivity!

#### Course

- 75% ADHD children continue to have disorder as adolescents, and 50% as adults.
- **hyperactive symptoms** may decrease with age (developmental self-control); **inattentive symptoms** do not appear to have similar developmental advantage and tend to remain constant into adulthood.

### ASSESSMENT INSTRUMENTS

Neuropsychological testing is not required to diagnose ADHD!

#### IQ tests

- untimed tests are most appropriate.
- large discrepancy between patient's IQ and other measures, such as visual or auditory abilities or ability to work with numbers, is not uncommon.
- many people in whom ADHD is not diagnosed until later years have **IQs well above average** but **function**, such as short-term memory, that is **at or below average**.
- perform learning-disability (LD) evaluation (**IQ** versus **academic achievement**).

#### Gauging:

1. **Conner's questionnaire** (administered to parents or teachers).
2. Written / computerized **tests of attention**.
3. **Accelerometer** on wrist
4. **Gauge** under seat of child's chair

### DIFFERENTIAL DIAGNOSIS

#### Conditions that may cause hyperactivity:

1. **Sedative-hypnotics** paradoxically cause hyperactivity in some children.
2. **Depression** - sad feelings may be expressed by increased activity.
3. **Anxiety**
4. **Severe CNS disease** (grossly abnormal CNS, significant head trauma).
5. **Constitutional hyperactivity** is present from birth.
6. **Factitious hyperactivity** - intolerant parent, teacher, or supervisor.
7. **Specific learning disabilities** may be associated with hyperactivity.
8. **Severe language disorders**
9. **Tourette disorder**

### PATHOPHYSIOLOGY, NEUROIMAGING

**Frontal cortex** and circuits linking them to **basal ganglia** are critical for executive function and, therefore, to attention and exercise inhibition.

- executive functions are major tasks of frontal lobes.
- MRIs in patients show *decreased activation (low arousal) of right mesial prefrontal cortex* during tasks that require inhibition of planned motor response and timing of motor response to sensory cue.
- MRIs in patients show *weakened activity in right inferior prefrontal cortex and left caudate* during task that involves timing of motor response to sensory cue.
- catecholamines are main neurotransmitters with frontal-lobe function (**dopaminergic** and **noradrenergic** neurotransmission are main targets for ADHD treatment).
- 10-year study by National Institute of Mental Health (NIMH) demonstrated that **brains of children and adolescents with ADHD are 3-4% smaller** (more severe ADHD symptoms, smaller frontal lobes, temporal gray matter, caudate nucleus, and cerebellum).

### EEG

Neuropsychiatric EEG-Based Assessment Aid (NEBA) System - FDA-approved, brain function – based medical device for use in diagnosis of ADHD in children aged 6-17 years.

- NEBA system calculates **ratio of theta and beta brain waves**, which is comparatively high in children and adolescents with ADHD.
- not meant to be used alone as a means of confirming presence of ADHD; but can be employed in combination with complete medical and psychological assessment to help confirm diagnosis / to indicate direction that further testing should take.
- NEBA device should not be used in individuals with a history of EEG abnormalities, seizure disorder, on anticonvulsants, or with a metal plate or device in the head

### EPIDEMIOLOGY

**PREVALENCE** in children **3-9%**, in adults  $\approx 4.4\%$ .

- **positive family history** rises risk significantly.
- **male-to-female ratio = 2-4 : 1** (underidentification in girls remains major concern).

### ETIOLOGY, GENETICS

**ADHD** is one of the most highly heritable of all psychiatric disorders (heritability 0.60-0.95)

- studies have revealed several genes associated with ADHD with effect on dopamine receptors, dopamine transport, and dopamine beta-hydroxylase.

### TREATMENT

Healthy **diet** with minimal, if any, **caffeine**.

- no evidence that avoidance of sugar, foods with red dye or rich in salicylates, and megadoses of vitamins help.

Because regular **physical activity** is important in improving concentration, it may be important component of therapy.

### BEHAVIORAL CARE

Despite symptomatic deficits, children must still be held accountable for their behavior and its consequences!

- **school / education interventions** (**traditional** classrooms and academic activities often exacerbate ADHD);
  - ADHD children concentrate better in **front row** than in rear.
  - **study carrels** [angl. darbo kabina] are helpful - block distracting stimuli.
  - **low student-teacher ratios** (i.e. one-on-one instruction or small groups).
  - frequent **breaks** with opportunity to move about.
  - teachers have important function - **periodic feedback** about child's school performance through use of standardized scales, narrative descriptions, and telephone follow-up.

- **psychotherapeutics.**

## PHARMACOTHERAPY

**Sedatives** should be avoided because some (notably phenobarbital) may precipitate ADHD!  
**Neuroleptics** are contraindicated!

### PSYCHOSTIMULANTS

- first-line agents for ADHD - effective and lack major adverse effects when used at therapeutic doses.
- increase amount of intrasynaptic **dopamine** and **norepinephrine** → stimulate areas of decreased activation to higher state of arousal.
- all are schedule II controlled substances; rate of abuse\* among patients is very low (but not zero!).  
 \*medication treatment of ADHD reduces risk of future substance abuse by almost 2-fold!

1. **METHYLPHENIDATE** (Ritalin, Methylin, Concerta) - one of safest pharmaceuticals used in children! (available for > 40 years). see p. A35 >>
  2. **DEXMETHYLPHENIDATE** (Focalin, Focalin XR) - pharmacologically active d-enantiomer of racemic METHYLPHENIDATE. see p. A35 >>
  3. **DEXTROAMPHETAMINE** (Dexedrine, Dextrostat) see p. A35 >>
  4. **MIXED AMPHETAMINE SALTS** (Adderall) - DEXTROAMPHETAMINE and AMPHETAMINE mixture.
  5. **LISDEXAMFETAMINE Dimesylate** (Vyvanse) - prodrug of DEXTROAMPHETAMINE.
  6. Magnesium **PEMOLINE** (Cylert); no longer produced due to risk of liver toxicity!
  7. **GUANFACINE** extended-release tablets (**nonstimulant** selective α2A-adrenergic receptor agonist) - FDA approved adjunctive to stimulants.
- drugs are available as:
    - 1) **short-acting, immediate-release** (IR) preparation
    - 2) **extended-release** preparations (e.g. continuous release [CR], sustained release [SR], osmotic-release oral system [OROS]) – preferable for chronic treatment (e.g. to avoid taking drug at school).
    - 3) **METHYLPHENIDATE** is also available as **transdermal patch**.
  - initiate at lowest available dosing once daily → increase every 3-4 days until response is noted or adverse effects emerge.
  - *learning* often is enhanced at low doses, but *behavior* improvement requires higher doses.
  - **drug holidays** should be tried on weekends, holidays, or during summer vacations.
  - **placebo periods** (for 5-10 school days) - to determine whether drugs are still needed.
  - **adverse effects**: anorexia and growth suppression (growth curves should be followed!!!), sleep disturbances, mild anxiety, rebound (e.g. posttherapeutic agitation, anger, lethargy); most individuals develop tolerance for adverse effects within few weeks (but tolerance does not develop to neurotransmission augmentation of ADHD-related neurochemistry).
 

N.B. stimulants, particularly METHYLPHENIDATE, have some risk for **sudden death**!
  - **contraindications** - narrow-angle glaucoma, hypertension, MAOI use, advanced arteriosclerosis, hyperthyroidism, motor tics (questionable! – tics are not CI in most guidelines) or Tourette syndrome (for “–phenidates”).
    - BP improves in some individuals with hypertension, whereas others simply need slight increase in antihypertensive dose.
    - tics may improve or worsen.
  - children should be **screened for heart problems with ECG** before getting “–phenidates”.
  - spectrums of therapeutic efficacy and adverse effects of all psychostimulants are similar, but for individual, therapeutic efficacy may vary greatly among drugs, preparations, or formulations (generic vs brand name).

Typically, 1/3 of ADHD patients do not respond / cannot tolerate this class of agents!

Nonresponders to one stimulant should start another stimulant trial; if two stimulant trials are unsuccessful → try second-line agents

### NONSTIMULANTS

- second-line agents; no abuse potential!

FDA approved:

1. **ATOMOXETINE** (Strattera) - **selective norepinephrine reuptake inhibitor (SNRI)**
  - effective in ADHD (may be used as alternative or adjunct to stimulants).
  - 5-10% patients are poor metabolizers → increased drug exposure.
  - cases of **reversible hepatic failure** have been directly attributed to atomoxetine.
  - **contraindications**: use of MAOIs within 2 wk, narrow-angle glaucoma.
2. **GUANFACINE extended-release** - **relatively selective central α-2A adrenergic agonist** – enhances (!) norepinephrine tone in prefrontal cortex (the way stimulants work) - ultimately enhances working memory.
  - highly tolerable and safe drug.
  - helpful in treating pediatric **hyperactivity**, tics.
  - reduced BP and reduced heart rate commonly appear upon drug initiation, along with somnolence, sedation, and fatigue, which tend to diminish over a 2-week period.
  - may be used cautiously (risk of ventricular fibrillation) with stimulants.
  - **CLONIDINE** is also central α-agonist but much less selective than GUANFACINE.

**Antidepressants** (**IMIPRAMINE**, **DESIPRAMINE**, **BUPROPION**, **VENLAFAKINE**) – helpful as adjunctive.

No-efficacy:

**MODAFINIL** in August 2006 received no-approval letter from FDA for treatment of ADHD!

**ST. JOHN'S WORT** - not more effective than placebo.